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Increasing Incidence and Age at Onset of Amyotrophic Lateral Sclerosis in Nagano Prefecture, Japan

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Background : A recent increase in the incidence of amyotrophic lateral sclerosis (ALS) has been reported in several countries. A similar trend was suspected for Nagano prefecture in Japan. Thus, we retrospectively examined the incidence of ALS and the characteristics of ALS patients at Shinshu University Hospital.

Methods : From hospital clinical records, we identified and enrolled 199 patients with ALS diagnosed based on the El Escorial criteria during the period 1985–2014. The 30-year period was divided into six terms of 5 years each. The incidence of ALS, sex ratio, subtype (limb- or bulbar-onset ALS), and age at onset (<65 or ≥ 65 years) were investigated separately for each term.

Results : The incidence of ALS significantly increased in the two most recent terms (2005–2009 and 2010–2014) overall, and in both men and women. A significant difference in mean age at onset was observed in the two most recent terms as compared with the first term (1984–1989). The increase in age at onset was particularly notable in the women with bulbar-onset ALS. No significant change was found in the proportion of ALS patients who were residents of the Matsumoto medical service area as compared with those from other areas.

Conclusion : We confirmed that the incidence of ALS in Nagano prefecture has been recently increasing. Furthermore, the ratio of patients with older-onset ALS has recently increased because of the chronological increase in age at onset of ALS patients. *Shinshu Med J 64 : 239—246, 2016*

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Key words : amyotrophic lateral sclerosis, incidence, Japan, population aging, onset

I Introduction

Amyotrophic lateral sclerosis (ALS) is the most common and well-recognized form of motor neuron disease. It is characterized by the progressive degeneration and subsequent loss of upper and lower motor neurons, which lead to weakness and paralysis of the upper and lower limbs, and facial, bulbar, truncal, and respiratory muscles[1)2)]. The phenotypic presentation is heterogeneous, with variable involvement of muscle groups and differences in prognosis and quality of life, probably reflecting the different mechanisms causing the disease[3)]. The involvement of bulbar and respiratory muscles is characterized by dysarthria, choking, ineffective cough, dyspnea, and progressive respiratory failure, which generally lead to death within 3 to 5 years of disease onset[4)5)]. The estimated incidence has been reported to be around 1–2 cases per 100,000 inhabitants per year. Only 5–10 % of cases are familial, with most of the cases being sporadic[4)].

Sporadic cases are clinically divided into bulbar- and limb-onset subtypes. In general, the progression is faster and the prognosis is poorer in patients with bulbar-onset ALS than in those with limb-onset ALS[6)]. The rate of invasive positive pressure venti

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lation (IPPV) introduction has been reported to range from 26.8 % to 40 % in ALS patients in Japan[7]. However, even with the use of IPPV, generalized muscle dysfunction continues to progress and, once extraocular movement is lost, leads to the loss of communication ability. This condition is called the totally locked-in state (TLS). In addition to the impact of this profound disability on daily life, introducing IPPV will increase both the burden of care and medical costs, which are socially important issues.

The cause of ALS is still unknown. However, some hypotheses concerning its pathogenesis have been proposed, including excitotoxicity, oxidative stress, impairment of neurofilament function, mitochondrial dysfunction, neuroinflammation, altered energy metabolism, RNA misprocessing, and the misfolding of certain proteins[1)8)9)]. Several case-control studies have analyzed risk factors of ALS, but their results are inconsistent[10)]. So far, riluzole (which protects neuronal cells from excessive glutamic acid) and edaravone (which removes free radicals) have been used to delay disease progression[11)]; however, no radical therapy has been developed.

In recent decades, several reports have described the increasing incidence of ALS. In Italy, Chio, et al. and Govoni, et al. showed a chronological increase in mortality from ALS[12)–14)]. We, too, suspect that a similar chronological increase in ALS incidence exists recently. Thus, the aims of this study were to determine whether the incidence of ALS has been increasing in Nagano prefecture or not and, if so, to identify factors associated with that increase. We conducted a retrospective epidemiological study focusing on the occurrence of ALS between 1984 and 2014 at our hospital.

II Subjects and Methods

A Study area

All the patients in this study lived in Nagano prefecture, which is located in the central region of Japan. This area has a stable population count, without much migration. It is racially homogenous and, much like the rest of Japan, has a progressively aging population. Our hospital serves as a referral center for other hospitals in the prefecture. Many of the patients with motor neuron disease are referred for consultation and further examination.

B Registry of ALS patients

We retrospectively analyzed the clinical records of 232 consecutive patients with ALS diagnosed at Shinshu University Hospital between 1985 and 2014. All the patients were consecutively consulted at our hospital and were interviewed by neurologists. The onset of illness was determined to be the time at which progressive muscle weakness in any body part was noticed, ascertained by conducting family and patient interviews and consultation with initial physicians.

Full neurological examination and neurophysiological diagnostic investigations (spinal tap, magnetic resonance imaging, needle electromyography, and nerve conduction velocities) were performed for each patient at registration to confirm the diagnosis. Each eligible case was then classified according to the revised El Escorial diagnostic criteria[15)]. We excluded 30 patients whose diagnoses were not confirmed by using the revised El Escorial diagnostic criteria and three patients who were assessed as having ALS with laboratory abnormalities of uncertain significance. Finally, the clinical records of 199 patients were studied (**Fig. 1**).

To investigate whether the incidence of ALS has recently been increasing or not, the 30-year period was divided into the following six terms of 5 years each: 1984–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2014. The incidence (stratified by sex) and subtype of ALS (limb- or bulbar-onset) were calculated for each 5-year term. The age at onset was also measured for each 5-year term.

C Statistical analyses

The age at onset was presented as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance to evaluate a statistical difference between the six terms. Intergroup comparisons were performed using Bonferroni correction. Statistical significance was set at $P < 0.05$.

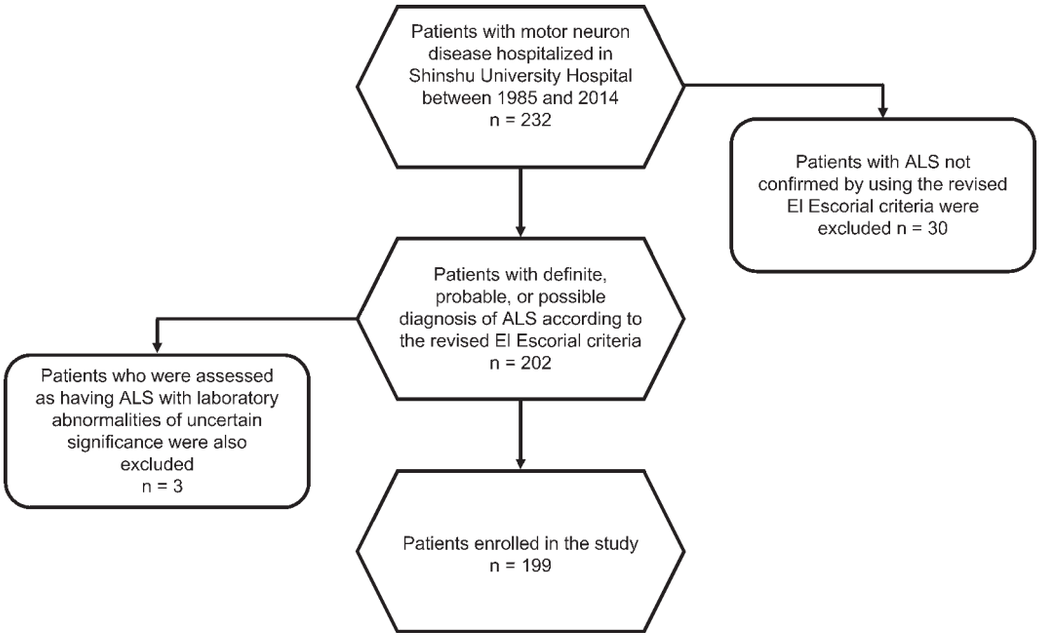

Fig. 1 A flowchart showing participant recruitment process. Of the 232 patients with motor neuron disease, 199 had definite, probable, and possible ALS according to the revised El Escorial diagnostic criteria and were included in the study.

D Others

This study was approved by the ethics committee of Shinshu University School of Medicine (permission No. 3403).

Ⅲ Results

A Characteristics of the patients

Of the 199 patients included, 115 were men and 84 were women. The mean age at symptom onset was 64.6 ± 12.2 years, and the mean time from symptom onset to diagnosis was 31.7 ± 46.1 months. Of the cases, 191 were sporadic and 8 were familial.

The patients were divided into two groups according to age as follows : a younger-onset group (<65 years old : 59 men and 36 women ; age range, 28-64 years) and an older-onset group (≥65 years old : 56 men and 48 women ; age range, 65-90 years).

Of the 199 patients, 149 had limb-onset ALS (90 men and 59 women ; mean age at onset, 62.2 ± 12.4 years ; mean time from onset to diagnosis, 36.7 ± 53.4 months) and 50 had bulbar-onset ALS (25 men and 25 women ; mean age at onset, 70.3 ± 9.8 years ; mean time from onset to diagnosis, 19.4 ± 13.0 months).

Of the 149 limb-onset ALS cases, 142 were sporadic, 7 were familial, 78 (52.3 %) were younger-onset, and 71 (47.7 %) were older-onset. Of the 50 cases of bulbar-onset ALS, 49 were sporadic, 1 was familial, 17 (34 %) were younger-onset, and 33 (66 %) were older-onset.

B Increased incidence of ALS in Nagano prefecture in the most recent 10-year period

The incidences of ALS in the five-year terms were as follows : 1984-1989, 18 patients (6 men and 12 women ; 12 limb-onset and 6 bulbar-onset) ; 1990-1994, 22 patients (14 men and 8 women ; 17 limb-onset and 5 bulbar-onset) ; 1995-1999, 26 patients (15 men and 11 women ; 20 limb-onset and 6 bulbar-onset) ; 2000-2004, 19 patients (9 men and 10 women ; 13 limb-onset and 6 bulbar-onset) ; 2005-2009, 50 patients (31 men and 19 women ; 40 limb-onset and 10 bulbar-onset) ; and 2010-2014, 64 patients (40 men and 24 women ; 47 limb-onset and 17 bulbar-onset), as shown in **Fig. 2A, B**. In the last decade, the mean incidence of ALS was 11.4 per year at our hospital, which is about three times greater than that in the decade 1985-2004 (4.25 per year). The incidence of ALS increased in both men and women in the last 10 years. In addition, the incidences of both limb- and bulbar-onset ALS have increased.

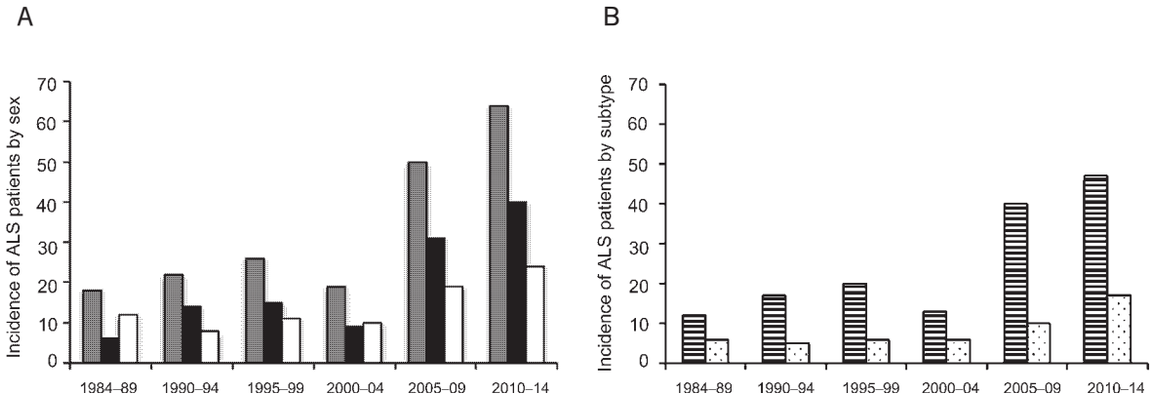

Fig. 2 The incidence of ALS in terms of 5-year intervals, from 1984 through 2014.
(A) Changes in incidence of all (gray columns), male (black columns), and female ALS patients (white columns).
(B) Changes in incidence of limb- (striped columns) and bulbar-onset ALS (dotted columns).

C Gradual increase in age at onset of ALS patients in Nagano prefecture

The ages at onset of all ALS patients in the 5-year terms were as follows: 55.3 ± 8.48 years in 1984-1989; 58.8 ± 12.6 years in 1990-1994; 62.2 ± 11.1 years in 1995-1999; 62.7 ± 12.9 years in 2000-2004; 65.3 ± 9.26 years in 2005-2009; and 66.2 ± 11.0 years in 2010-2014. The mean age at symptom onset tended to rise year on year, being significantly higher in 2005-2009 and 2010-2014 than in 1984-1989 (**Fig. 3A**).

The proportions of patients with older-onset ALS in comparison with those of patients with younger-onset ALS were as follows: 3 (17 %) versus 15 (83 %) in 1984-1989; 9 (41 %) versus 13 (59 %) in 1990-1994; 14 (54 %) versus 12 (46 %) in 1995-1999; 11 (58 %) versus 8 (42 %) in 2000-2004; 29 (58 %) versus 21 (42 %) in 2005-2009; and 38 (60 %) versus 26 (40 %) in 2010-2014. The ratio of the patients with older-onset ALS to those with younger-onset ALS has increased chronologically, with older-onset ALS accounting for more than half of the new cases since 1995 (**Fig. 3A**). Furthermore, in women and bulbar-onset ALS, the age at onset was particularly high in the two most recent terms than in the first term (1984-1989; **Fig. 3B, C**).

D No significant difference in residential area of ALS patients among the 5-year terms

Nagano prefecture has 10 medical service areas, including our university hospital, which is located in the center of the Matsumoto medical service area (**Fig. 4A**). The proportions of ALS patients who were residents of the Matsumoto medical service area in comparison with those of ALS patients from other areas were as follows: 11 (61 %) versus 7 (39 %) in 1984-1989; 8 (36 %) versus 14 (64 %) in 1990-1994; 12 (46 %) versus 14 (54 %) in 1995-1999; 7 (37 %) versus 12 (63 %) in 2000-2004; 23 (46 %) versus 27 (54 %) in 2005-2009; and 30 (47 %) versus 34 (53 %) in 2010-2014. The differences in these proportions among the 5-year terms were not statistically significant ($P = 0.6971$; **Fig. 4B**).

Ⅳ Discussion

In this study, we found that the incidence of ALS has increased and that the age at onset of ALS has also became older over the past decade (2005-2014) at our hospital. In particular, the age at onset among female patients and among patients with bulbar-onset ALS were significantly higher during this period than 30 years ago.

The mortality from ALS has been reported to have increased in Italy. According to the Italian report, the mortality rate was 0.8 per 100,000 people prior to 1980 but increased to 1.4 per 100,000 people after 1990[12]. In general, the prognosis of ALS is poor and the time from diagnosis to death is relatively short. Therefore, chronological increases in the number of deaths most likely reflect the increased incidence of ALS. In our study, we found

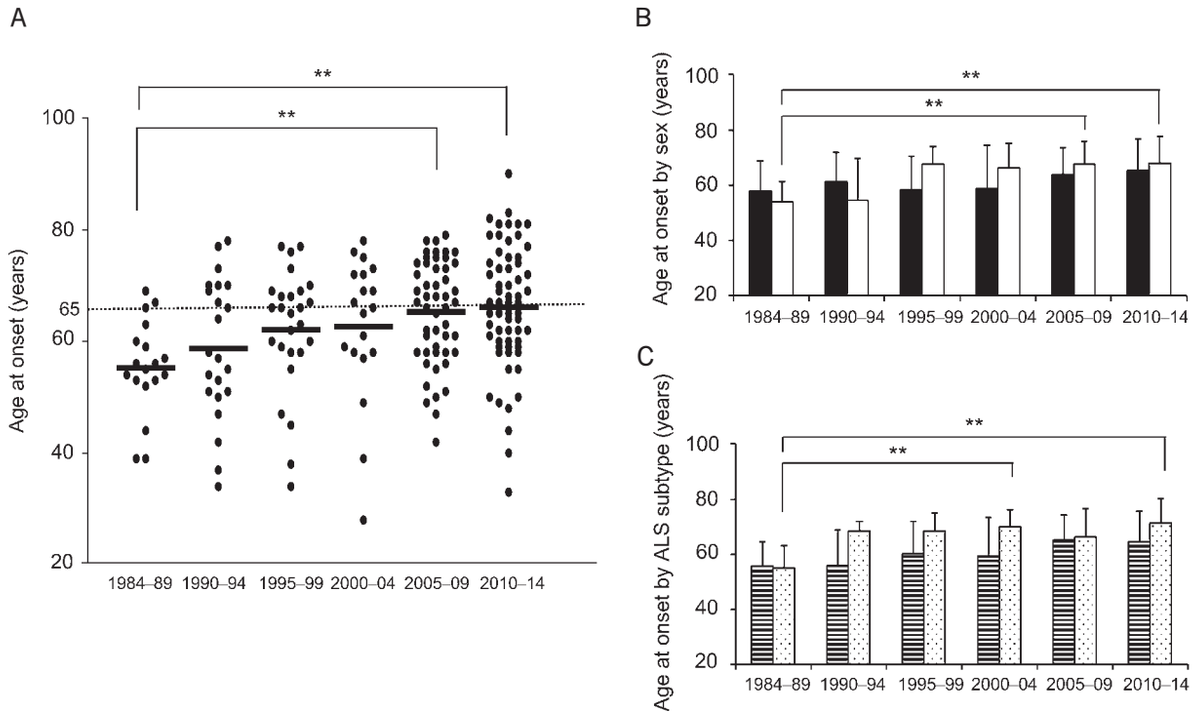

Fig. 3 Changes in the age at onset of ALS patients in terms of 5-year intervals, from 1984 through 2014.
(A) Dot plots of the age at onset of all the ALS patients. The horizontal lines indicate the mean value of all determinations. $^{**}P<0.01$.
(B) Changes in mean age at onset of the male (black columns) and female patients (white columns). Bar : mean ± SD. $^{**}P<0.01$.
(C) Changes in the mean age at onset of the patients with limb- (striped columns) and bulbar-onset ALS (dotted columns). Bar : mean ± SD. $^{**}P<0.01$.

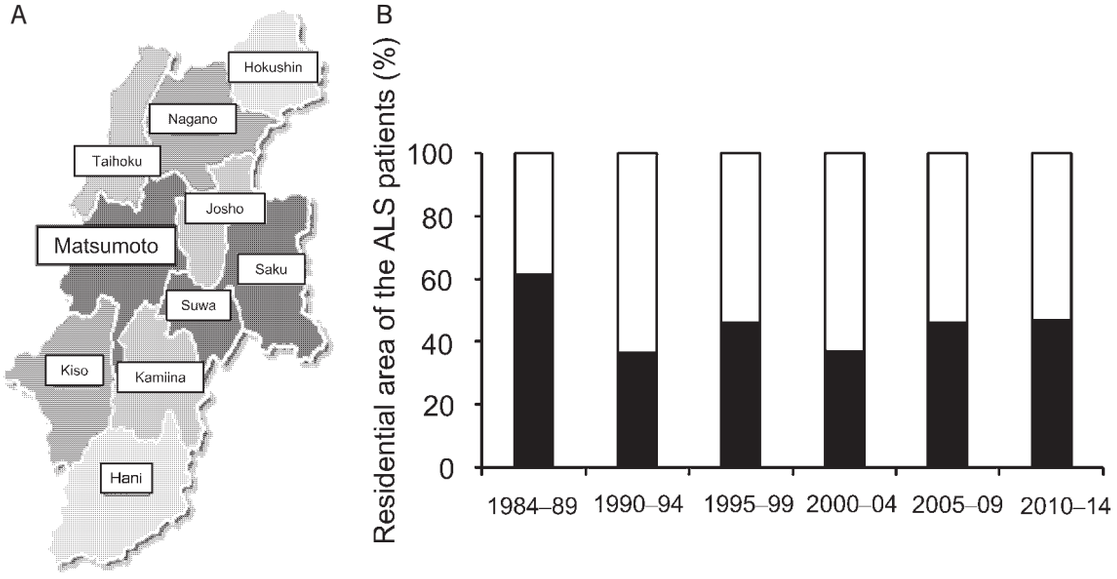

Fig. 4 Changes in the proportion of all the ALS patients who were residents of the Matsumoto medical service area or other areas in Nagano prefecture.
(A) The ten medical service areas in Nagano prefecture. The Matsumoto medical service area is located in the central region of Nagano prefecture.
(B) The black columns indicate the patients who were residing in the Matsumoto medical service area, and the white columns indicate the patients who were residing in other areas.

that the incidence of ALS increased chronologically in Nagano prefecture, with a 2.5-fold greater incidence in the period 2005-2014 than in 1996-2003. Thus, the incidence of ALS has increased abruptly in the last 10 years.

Recently, obtaining a definite diagnosis of ALS has become possible in many local hospitals outside of the Matsumoto medical service area due to the advancement of diagnostic techniques and the supply of neurologists trained at Shinshu University Hospital. Therefore, a large number of ALS patients would not have been introduced to Shinshu University Hospital. Nevertheless, the number of ALS patients continues to increase in the Matsumoto medical service area. In addition, no significant change was observed in the proportion of ALS patients who were residents of the Matsumoto medical service area as compared with that in other areas between 1984 and 2014 (**Fig. 4B**).

Furthermore, ALS is a rare disease that shows characteristic symptoms/signs and clinical course along with disease progression. Thus, almost all ALS patients seek medical care and can be diagnosed as having ALS by neurologists. This situation has not changed in 30 years. Therefore, we considered that the increased incidence of ALS in the last 10 years was caused by the increase in the incidence of ALS in both the Matsumoto medical service area and other areas, and not by an inflow of patients from other medical service areas or by an increase in the total number of people visiting Shinshu University Hospital. This suggests that the incidence of ALS has been increasing in Nagano prefecture.

An autopsy investigation conducted in Niigata prefecture (which adjoins Nagano prefecture) showed an increase in both the incidence of ALS and age at onset of patients with ALS diagnosed in the period 1990-2000 as compared with the period 1962-1970[16]. This is consistent with our results. We suppose that this trend of increased incidence of ALS will be seen throughout Japan.

Having identified an increase in the incidence of ALS, we then need to consider the reasons for this increase in recent years. Based on demographic statistics from Nagano prefecture[17], the aging population is increasing at a constant rate (as seen in other prefectures). However, the rate of increase in the population aged ≥65 years displays a linear function (**Fig. 5**). By contrast, our data revealed that the rate of increase in the incidence of ALS displays a quadric function. Thus, in addition to an increasingly aging population, other factors may be associated with the increased incidence of ALS.

In addition, our study demonstrated that the ages at onset in women and in patients with bulbar-onset ALS were significantly higher in the past decade than in the period 1984-1989. A significant decrease has been reported in the male-to-female ratio, which reduced from 1.8-2.6 : 1 in the decade 1959-1974 to 1.1-1.3 : 1 in the 1990s. The decrease in the male-to-female ratio is particularly apparent in older-onset ALS, between 2.9 : 1.4 and 6.6 : 1.5 in 1959-1974 falling to between 10.2 : 7.4 and 10.4 : 8.6 in the 1990s[18]. This indicates that, especially in older-onset ALS, the incidence of ALS has increased disproportionately in women. These data are consistent with our results that the age at onset of female ALS patients, in particular, has been increasing in recent years.

Why has the incidence of ALS been increasing more especially in patients with older- and bulbar-onset ALS in recent years? The following possible hypotheses are considered : 1) In the past, patients who may have developed ALS might have died from other causes before the onset of typical symptoms or diagnosis of ALS was made, but owing to the increased life spans, the symptoms now become clinically evident. 2) Neck and bulbar muscles are naturally weakened in older individuals, making bulbar symptoms more evident at the onset of older-onset ALS.

Considering that Japan's population is progressively aging, the increased incidence of older-onset ALS could result in various social problems. As the progression of ALS is generally rapid and the associated burden of care and medical costs are not insignificant, ALS has an important impact on

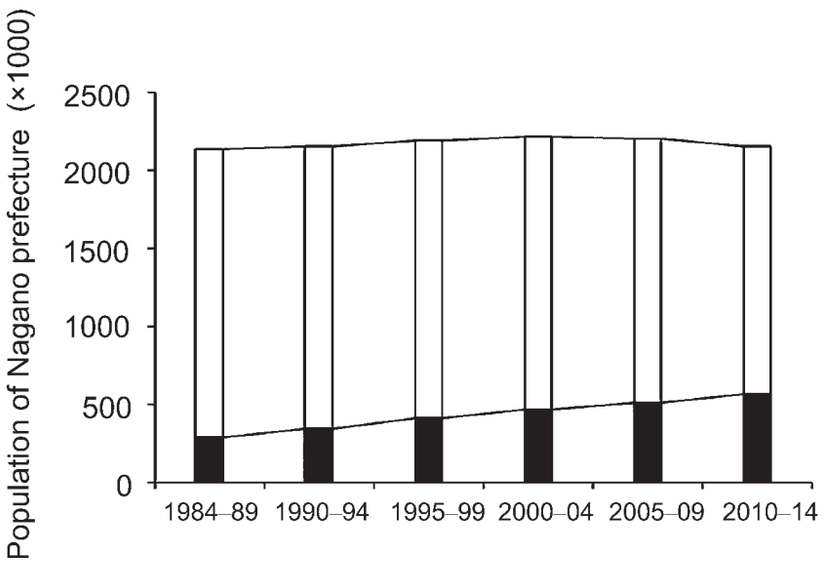

Fig. 5 Changes in the population of Nagano prefecture. The black columns indicate the population aged ≥65 years, and the white columns indicate the population <64 years (16).

patients' families, the medical community, and public welfare systems. Aged ALS patients can easily develop many complications, some of which can be managed by means of interventions such as gastrostomy and home-based IPPV. However, these interventions cannot prevent disease progression. The care needs of the aging population, in the context of a population with a progressively declining birth rate, lead to difficulty in providing home care. Moreover, spaces in medical institutions and rest homes for ALS patients are limited, especially in regional towns and cities. Thus, we should bear in mind the need to establish a medical framework for patients with older-onset ALS. Enhancement of home care systems and institution of support systems to assist in decision making on interventions such as gastrostomy and home-based IPPV are desirable. In addition, guidelines on the medical care of (older) ALS patients should be prepared for general physicians.

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Disclosure

All authors report no disclosures.

Conflict of interest : None to report.

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